CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-146

Medical Review(s)

MORGENSTERN

SEP 18

9/18/00

TO: NDA 21146, Atropine Sulphate Injection in Plastic Syringes

From: Stephen Fredd, MD, HFD-110 SF 9/18/00

Subject: Review and Evaluation

I. Background

On 12/16/99 Abbott submitted an NDA under Section 505(b) 2 of the Act for Atropine Sulphate injection in plastic syringes. They have been marketing the pre-1938 drug Atropine Sulphate injection in glass for the following indications:

1. Antisialogogue for preanesthetic medication to prevent or reduce respiratory tract secretions.
2. To restore cardiac rate and arterial pressure during anesthesia when vagal stimulation produced by intra-abdominal surgical traction causes a sudden decrease in pulse rate and cardiac action.
3. To lessen the degree of A-V block when increased vagal tone is a major factor in the conduction defect as in some cases due to digitalis.
4. To overcome severe bradycardia and syncope due to hyperactive carotid sinus reflex.
5. As an antidote for cardiovascular collapse (with external cardiac message) from the injudicious use of a choline ester (cholinergic) drug.
6. In the treatment of anticholinesterase poisoning from organophosphorous insectisides.
7. As an antidote for the "rapid" type of mushroom poisoning due to muscarine in certain species of fungus such as Amanita muscaria.

For the product in plastic the same indications were requested.

On May 12, 2000 the sponsor amended the application with additional references, organized and summarized by indication, and new proposed labeling with the following additional requested indications:

8. For the treatment of Type II second degree and complete AV block, symptomatic bradycardia and asystole.
9. To block the muscarinic side effects of anticholinesterase drugs used for reversal of neuromuscular blockade.
10. To restore cardiac rate and arterial pressure during anesthesia when vagal stimulation produced by ocular muscle or other surgical traction causes a sudden decrease in pulse rate and cardiac action.

Two parenteral Atropine Sulphate products have been approved. The first, AtroPen autoinjectors for the management of patients who suffered a toxic exposure to organophosphorous or carbamate insectides, and the second a fixed combination of edrophonium and Atropine to reverse the effects of nondepolarizing neuromuscular blocking agents.

The AtroPen approval was brought to the sponsor's attention at a meeting on February 16, 2000, as well as the need for adequate and well-controlled studies for other indications. It was noted that under 21CFR 314.54(a) where there was an approved product and the same indication was being sought, a sponsor need submit only those investigations that supported the differences in labeling being requested.

This review will consider what the sponsor has provided in support of the indications, populations and dosage in a somewhat revised order.

II. Groupings of Requested Indications

i. Treatment of Poisonings

a. Organophosphorous insecticides

10 reprints were provided.

1. Drug Safety 1997 Jan: 16 (1) 9-47. Clinical Applications of Commonly Used Contemporary Antidotes. A chapter from a textbook by Bowden and Kenzelok which suggests a dosing regimen of 2 mg IV every 10-30 minutes for moderate poisoning and 2-5 mg IV every 10-30 minutes for severe poisoning. The authors note that the presence of preservatives such as benzyl alcohol or chlorobutanol may produce toxicity, and recommend the use of preservative free drug. Most common side effects are noted to be cholinergic such as disorientation, tachycardia and dilated or unresponsive pupils.

2 JAMA, August 4, 1989; 262:649-652. Dunn and Sidell, Progress in Medical Defense against Nerve Agents.
Discusses military use of Atropine autoinjectors. Notes use of Atropine with oximes such as pralidoxime to complex with acetylcholinesterase-bound nerve agents.

3 Pharmacotherapy, 4th edition, 1999,Appleton & Lange, p.80,81,88-90. Clinical Toxicology.
Selected pages describing management of organophophate poisoning with Atropine and pralidoximine. Doses suggested: 0.05-0.1mg/kg IV in children under 12 years of age; 2-5mg in adolescents and adults.

4 JAMA, vol. 159 (12), Nov. 19,1958, p.1181-1184, Gordon and Frye. Large doses of Atropine.
Authors note that Atropine should be used to combat the muscarinic and cns effects of organophosphate, and reviewed 149 case reports of poisoning in the literature of which 25 had sufficient data on dose to evaluate whether large doses were better than small. Those who survived received Atropine earlier and in larger cumulative amounts than those who died. The authors also searched the literature for data on the toxicity of large doses of Atropine, and prented the information on 11 deaths from a survey of approximately 1000 cases. They conclude that an initial dose of 2 mg is recommended with additional doses hourly or more frequently depending on the persistence of muscarinic effects.

5 Pediatric Clinics of North America, Vol.17, No.3, 1970, p.629-644, Hayes. Epidemiology And General Management of Poisoning by Pesticides.
For 1968 there were 2919 cases of insecticide poisoning reported of which 1858 were in children under intervals. Recommends 2-4mg IV of Atropine after cyanosis is treated with additional doses at 5 to 10 minute intervals until signs of atropinization appear (dry, flushed skin, tachycardia). Mild atropinization should be continued for 24-48 hours. The children's dose recommended is 0.05 mg/kg IV.

6 Journal of Emergency Nursing, vol.8, No.6, Nov/Dec 1982, p.288-294, Miller. Pesticide Poisoning.
Describes an Atropine test to determine if there has been pesticide poisoning. 2 mg of Atropine is given IV. If sympathomimetic effects appear, pesticide poisoning unlikely. For treatment, 2 mg IV is recommended for adults every 5 to 10 minutes until a pulse rate of 120 bpm and mydriasis occurs. The dose is children is given as 0.05 mg/kg IV.

7 Principles and Practice of Anesthesia, 1993, Mosby, p.1502-150. Basic Physiology and Pharmacology of the Autonomic Nervous System.
Short description of the actions of Atropine.

8 American Family Physician, vol. 9 (5),p.146-148, Sim. Anticholinesterase Poisoning.
Describes signs and symptoms of organophosphorous and carbamate poisoning, and recommends Atropine doses of 2-4 mg IV.

9 Toxicology Letters 107 (1999), p. 233-239, Thiermann et al. Modern Strategies in Therapy of Organophosphorous Poisoning.
While mentioning Atropine therapy, this article deals mainly with oxime therapy.

10 New England Journal of Medicine, Aug. 18, 1955, p.266-271, Freeman and Epstein.
Therapeutic Factors in Survival After Lethal Cholinesterase Inhibition by Phosphorous Insecticides.
The case reports of 46 patients who had ingested lethal amounts of phosphorous insecticides were analyzed for survival relative to therapy given. 41 had ingested Parathion; 5 tetraethylpyrophosphate. 18 of the Parathion patients died; all of the tetraethylpyrophosphate patients died.
The authors classified the outcome by type of treatment as follows:

Type of Treatment	No. of Cases	Survivors
Dual treatment, early and adequate Atropine +Artificial Resp. and O2	10	10
Palliative Atropine, followed by Delayed adequate treatment	7	7
Early & Adequate Atropine alone	3	3
Dual Treatment late but Vigorous	1	1
O2 Treatment mainly with Token Atropine	1	1
Tracheotomy & Manual Artificial Respiration	1	1
Initially Effective Atropine without Adequate Maintenance	5	0
Atropine or Ventilatory Treatment Late & Inadequate	8*	0
None	10‡	0
Total	46	23

*Includes 2 cases of tetraethypyrophosphate poisoning
‡Includes 3 cases of tetraethylpyrophosphate poisoning

Also presented was a comparison of survivors and fatalities for the total amount of Atropine given during the first 5 hours of therapy.
The authors conclude that Atropine given promptly in quantities greater than 3 mg within the first five hours with supportive ventilation was lifesaving.

b. Mushroom Poisoning

2 reprints were provided.

1. JAMA, vol.251 (8), Feb. 24,1984; p. 1057-1061, Hanrahan and Gordon. Mushroom Poisoning; Case Reports and a Review of Therapy.
   None of the 4 case reports mention treatment with Atropine. While the rapid- acting mushroom toxins may affect the autonomic system producing cholinergic symptoms, the authors recommend that Atropine be given only to severe cases.

2. Acta Anaesthesiol Scand 1988: 32: 69-78, Kanto and Klotz. Pharmacokinetic Implications for the Clinical Use of Atropine, Scopolomine and Glycopyrrolate.
   This interesting article provides summary information from articles in the literature (including Virtanen et al, Acta Anesthesiol Scand 1982; 26, p. 297-300 that is cited in the approved edrophonium plus Atropine labeling) on the PK of Atropine given orally, rectally, by inhalation, IM and IV in adults, children and the elderly. Some charts from the article are provided below:

Important pharmacokinetic parameters following i.v. injection of atropine in adult subjects (mean ± s.d.).

Age (years)	N	t_{α} (min)	t_{β} (h)	V_1 (l/kg)	V^{β} (l/kg)	Cl (ml/min/kg)	Reference
21–29	10	1.0 ± 0.1	2.6 ± 0.5	0.13 ± 0.03	1.0 ± 0.1	6.4 ± 1.8	44
16–58	8	1.7 ± 1.4	3.0 ± 0.9	0.09 ± 0.05	1.6 ± 0.4	6.8 ± 2.9	27
28–71	8	1.2 ± 0.6	4.3 ± 1.7	0.20 ± 0.17	1.7 ± 0.7	5.9 ± 3.6	21
27–39	6	–	4.1*	46.0 ± 20.7†	290.8 ± 145.4†	533.4 ± 309.6††	24
21–24	3	1.0 ± 0.2	2.2 ± 0.6	19.1 ± 9.1†	210 ± 27†	1175 ± 202††	18

t_{α} = distribution half-life; t_{β} = elimination half-life; V_1 = volume of the central compartment; V^{β} = total apparent volume of distribution; Cl = total serum or plasma clearance.
*only the mean value was reported.
† = l; †† = ml/min.

Pharmacokinetic parameters of atropine in children and in the elderly over 65 years of age; for comparison, adult values are included (27, mean ± s.d.).

Age	N	t_{β} (h)	V^{β} (l/kg)	Cl (ml/min/kg)
Under 2 years	7	6.9 ± 3.3	3.2 ± 1.5	6.8 ± 5.3
Over 2 years	6	2.5 ± 1.2	1.3 ± 0.5	6.5 ± 1.6
Adults	8	3.0 ± 0.9	1.6 ± 0.4	6.8 ± 2.9
Elderly	10	10.0 ± 7.3	1.8 ± 1.2	2.9 ± 1.9

The authors cite some data on IM administration and note that there is a great deal of interindividual variation in Tmax and Cmax.
No specific information on mushroom poisoning is provided in this article.

c. Chlorinergic Drug-Induced Cardiovascular Collapse

No references provided.

ii. Uses in Anesthesia

a. Antisialogogue

10 reprints were provided to support the indication.

1. Journal of Clinical Pharmacology, vol. 22, 1982, p. 477-481, Adams et al. Plasma Pharmacokinetics of Intravenously Administered Atropine in Normal Subject. Study of PK/PD in 6 normal male volunteers given 1 mg of Atropine IV. Mean terminal half-life was 4.125 hours, and correlation of changes in pulse and tissue levels of Atropine was suggested. No information specific to this indication was provided.

2. Pediatric Emergency Care, vol.12, No.6, December 1996, p.435-441, Algren and Algren. Sedation and Analgesia for Minor Pediatric Procedures. Mentions "An anticholinergic, either Atropine or glycopyrolate, should be administered with ketamine to prevent hypersalivation."

3. The Pediatric Anesthesia Handbook, second edition, Mosby, p. 26,27, 30, 31, 32,33, 608,609. Various authors. Notes that current inhalation anesthetics do not cause hypersalivation, and therefore anticholinergic drugs are not routinely indicated and if used may cause fever, confusion, flushing or dry mouth. During surgery if an antisialogogue is needed, Atropine 0.02 mg/kg IM or PO, 0.01 mg/kg IV may be given.

4. Geriatrics:22 (9), September, 1967, p.115-121, Inglis. Premedication in the Geriatric Patient. States that routine premedication with Atropine is not recommended, but is indicated if drugs that stimulate the parasympathetic or ether are to be used.

5. Anesthesia and Intensive Care, vol. II, No. 1, February, 1974, p.77-80, Kessell. Atropine Premedication. This was a randomized, double blind study of atorpine 0.6 mg versus no Atropine in premedication solution containing pethidine 100 mg and promethizine 25 mg. 125 adult patients (51 assigned to Atropine, 74 to no Atropine) who were to undergo routine anesthesia given by the author were entered. Those having intraorbital or intraoral procedures, the very ill or those with established cardiac arrhythmias were excluded. No significant differences for age or sex were noted between the two groups. Some principal findings were given in the following charts from the publication.

The Number of Patients and the Incidence of Arrhythmias

	Number of Patients	Ventricular Arrhythmias	Supraventricular Arrhythmias	Arrhythmias during Induction
Atropine	51	9 (17·6%)	6 (11·7%)	15 (29·4%)
Non-atropine	74	17 (22·9%)	9 (12·1%)	26 (35·1%)
Total	125	26 (20·8%)	15 (12·0%)	41 (32·8%)

The Incidence of Arrhythmias during Laryngoscopy Endotracheal Intubation

	Patients Intubated	Laryngosc and Intubatio Arrhythmi
Atropine	36	11 (30-5%)
Non-atropine ..	51	20 (39-2%)
Total	87	31 (35-6%)

Number of Patients and the Incidence of Postoperat Problems

	Number of Patients	Salivation	Vomiting	Laryngeal Spasm	Cough
Atropine ..	39	2	2	1	1
Non-atropine ..	40	3	1	0	0
Total ..	79	5	3	1	1

The author notes that there were no significant differences found, but notes that 5 cases of bradycardia appeared in the no Atropine cases versus none (NS) in those premedicated with Atropine. He states that the bradycardia was easily treated with Atropine when it occurred. The author concludes that the routine use of Atropine as premedication when non-irritating anesthetics are used is not supported by this study.

6. British Journal of Anesthesia, 51, 1979, p. 339-345, Mirakhur et al. Studies of Drugs Given Before Anaesthesia XVII: Anticholinergic Premedicants.

This study in 19 groups of 20 patients included those undergoing minor gynecologic surgery or ect. Atropine, hyoscine, glycopyrronium and placebo were used by both oral and im routes, using a double-dummy approach for blinding. Doses of Atropine were 0.5 mg, 1.0 mg, and 2.0 mg by each route. Heart rate changes and bronchial secretions were evaluated before and during the procedures.
All doses of im Atropine produced a significant increase in heart rate, but only the 1.0 and 2.0 mg oral doses produced an increase. All doses of IM Atropine produced significant subjective dryness at 60 minutes with an increase at 90 minutes, while all oral doses produced significant dryness at 90 minutes. These subjective results did not correlate with a smoother conduct of anesthesia. The authors conclude that routine use of such preanesthetic medication does not appear to be needed.

7. The Lancet, May 29, 1976, p.1148-1150, Prescott et al. Double-Blind Clinical Trial of Anesthetic Premedication for Use in Major Day Surgery.

158 patients who underwent surgery for varicose veins or hernia were randomly assigned to Atropine 0.6 mg , Atropine plus diazepam, or Atropine plus droperidol (route not specified). Various symptoms were evaluated postoperative as well as the postoperative use of analgesia, and the combination of Atropine and droperidol was better than Atropine alone or Atropine plus diazepam for nausea, vomiting and the need for analgesia.

8. Principles and Practice of Anesthesiology, Rogers MC, 1995, Mosby, p.52-58.
Pages from a textbook stating that in selected cases the antisialogogue effect of anticholinergic drugs may be important in the pediatric age group.

9. Clinical Pediatrics, September 1966, vol. 5, No. 9, p.549-553, Seigne. Premedication for Children Undergoing Anesthesia
The author suggests that either Atropine or scopolamine could be given to prevent excessive secretions or to protect the cardiac vagus. For Atropine doses of 0.1 to 0.6 mg are suggested depending on age.

10. General Dentistry, January-February,1999, p. 56-60, Sherman. Atropine Sulphate-a Current Review of A Useful Agent for Controlling Salivation during Dental Procedures.
Discusses use of Atropine Sulphate tablets to reduce salivary flow during certain dental procedures, and notes its contraindication in glaucoma.

b. Adjunct with Other Drugs to Reverse Neuromuscular Blockade

4 reprints were provided.

1. Journal of Post Anesthesia Nursing, vol 4 (2), April 1989, p. 112-115, Glass. Reversal of Muscle Relaxants.
The author describes the use of muscle relaxants that block the action of acetylcholine during surgery and their reversal by anticholinesterases such as neostigmine. Atropine was recommended for administration with the anticholinesterase to block the action of acelycholine at sites other than skeletal muscle such as the heart, salivary glands and bronchioles.

2. Anesthesia, 4th Edition, New York, Churchhill Livingstone, 1994, Moss and Craigo, chapter 16. The Autonomic Nervous System.
The textbook describes the pharmacology of Atropine and notes that the 1-2 mg doses used to block the muscarinic effects of anticholinesterase drugs can produce CNS effects.

3. Principles and Practice of Anesthesiology, St. Louis, Mosby, 1993, Rogers et al, p. 2180-2186. Chapter83: Anesthesia for Children.
Author recommends doses for children as follows: For neostigmine, give Atropine15-30 ug/kg for edrophonium, 10-20 ug/kg. No dose less than 0.15 mg should be given, and the Atropine should preceed the anticholinesterase.

4. Pediatrics, vol 52 (3), 1973, Rumack, p.449-451. Anticholinergic Poisoning: Treatment with Physostigmine.
Describes use of physostigmine in anticholinergic poisoning, and states that if toxic cholinergic symptoms occur, Atropine in half the physostigmine dose can be used.

iii. Cardiovascular Uses

a. AV conduction disorders, bradycardia, asystole, cardiopulmonary resuscitation.

26 reprints were provided.

1. British Medical Journal, August 23,1969,p.458-459, anonymous. Drugs for Cardiac Arrhythmias-II. States that Atropine Sulphate is of value in the management of bradyarrhythmias and heart block after MI. Suggests giving the drug in "small aliquots (0.3 to 0.6 mg).

2. The Washington Manual of Therapeutics, 29th edition online, 1998, chapter 7, Botterton and Smith. Discusses diagnostic criteria for cardiac arrhythmias such as bradycardia, A-V block.

3. American Heart Journal, vol 78 (1), p. 124-127, 1969, Cooper and Freiden. Atropine in the Treatment of Cardiac Disease.
Discusses clinical pharmacology of Atropine. Therapeutic dose of IV Atropine said to be 0.4 to 2 mg. In small doses IV or SC paradoxical cardiac slowing may occur.

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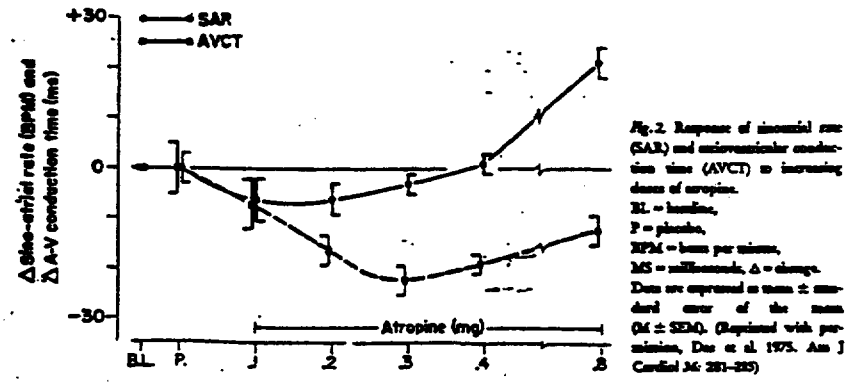
4. International Journal of Clinical Pharmacology, Therapy and Toxicology, vol 27 (10), 1989,p.473-477, Das. Cardiac Effects of Atropine in Man: an Update.
Review of cardiovascular pharmacology of Atropine. Response of sinoatrial node and AV conduction time to increasing Atropine doses displayed in the following chart.



5. Anesthesiology, vol 44 (6), 1976, p. 501-518, Dauchot and Gravenstein. Bradycardia after Myocardial Infarction and its Treatment with Atropine.
Review article describing the frequency, etiologies and risks of bradycardia post-MI. While the authors state that Atropine may be useful in certain circumstances such as bradycardia with hypotension, it is not needed in all cases, and has toxicity. In the elderly the authors note that there is a diminished or negative chronotropic response to Atropine, and even with dose titration the response is variable.

6. British Medical Journal, vol 3, 1967, p. 661-662, Navab and Honey. Self-poisoning with Digitalis Glycosides.
Two cases of digitalis intoxication with bradycardia both treated with Atropine were presented. One lived; one died.

7. The Lancet, Nov. 23,1969, p. 1097-1101, Adjey et al. Incidence, Significance, and Management of Early Bradyarrhythmia Complicating Myocardial Infarction.
The records of 550 patients with acute myocardial infarction managed by the Belfast mobile unit were reviewed. The sites of the infarcts were: anterior-259, posterior-262, combined-14, subendocardial-14, unknown-11. 126 patients experienced bradyarrhythmia (heart rate 60 BPM or less) that occurred more frequently in those with posterior infarcts. Atropine in aliquots of 0.6 mg IV was given to all with bradyarrhythmia, and responses in heart rate and BP (if hypotension was present) were noted. A variable effect on AV conduction was found.

8. The Lancet, Nov.23, 1969, p.1097-1101, Norris. Bradyarrhythmia Complicating Myocardial Infarction.
A letter to the editor discussing an article by Adgey et al (The Lancet, 1968,ii,p.1097). In this letter the author concludes: " Thus, although Atropine may improve the rhythm in some cases, it does not necessarily follow that this is of great benefit to the patient."

9. The American Journal of Cardiology, vol. 37, 1976, p. 68-72, Warren and Lewis. Beneficial Effects of Atropine in the Pre-hospital Phase of Coronary Care.

The study conducted over a 15 month period beginning in1968 was a record review of 70 patients with suspected acute MI and bradyarrhythmias given pre-hospitalization care in the Columbus, Ohio Heartmobile . The characteristics of these 70 were:

Clinical Characteristics of 70 Patients With AMI and Bradyarrhythmia Seen in Pre-Hospital Phase

Age (yr), 73% 65 or less	
Sex, 84% male	
Location of AMI	
Inferior	63%
Anterior	16%
Uncertain	21%
Interval from onset of symptoms to arrival of MCCU	
<30 minutes	30%
30 to 60 minutes	26%
>1 hour	44%
Incidence of hypotension*	
All patients	37%
HR 50 or <	53%

*Systolic blood pressure less than 100 mm Hg.
AMI = acute myocardial infarction; HR = heart rate; MCCU = mobile coronary care unit.

45 patients were given Atropine IV (average dose 0.86 mg; range 0.4 mg-2.0 mg); 25 were not. The reasons for the decision to treat were not specified, but were "not always in conformity with hospital policies."

The mortality results by normal BP or systolic BP <100 mm Hg were:

Mortality Rate in Patients With Bradyarrhythmia in the Pre-Hospital Phase of Acute Myocardial Infarction

Systolic Blood Pressure (mm Hg)	Treatment	HR	Mortality Rate (%)
Normal (23)	Atropine	80 ± 8 (SD)	13
Normal (21)	0	83 ± 7	14
<100 (16*)	Atropine	47 ± 10	25
<100 (6)	Atropine isoproterenol	33 ± 9	33
<100 (4)	0	51 ± 5	75

*Nine patients were restored to normal blood pressure and heart rate (mortality 11 percent).
Figures in parentheses indicate number of patients.
HR = mean heart rate (beats/min); SD = standard deviation.

From this chart one can deduce that the overall mortality rate was 20% in those treated with Atropine, and 24% in those not treated.

The authors note that patients with second and third degree heart block did not have a satisfactory response to Atropine alone, therefore isoproterenol was added. They conclude that Atropine is given to those in the early phases of an MI complicated by bradycardia and hypotension or ventricular arrhythmia.

10 American Journal of Hospital Pharmacy, vol. 42, Nov. 1985, p.2478-2483, Batenhorst et al. Evaluation of 516 Cardiopulmonary Resuscitation Attempts.
Record review of 516 adult cardiopulmonary arrests and resuscitation attempts at a tertiary care institution over a 24 month period was performed. Atropine Sulphate was given to 46.5% of the patients and was considered an essential drug by the AHA.

11. Emergency Medicine Clinics of North America, vol. 1 (3), Dec. 1983, p. 553-569, Boike and Rybak. Pharmacologic Interventions in Resuscitation.
States that Atropine is useful in the management of bradydysrhythmias. Notes that small doses may potentiate conduction disturbances, and large doses have been associated with agitation, disorientation and coma.

12. Emergency Clinics of North America, vol. 167 (2), 1998, p. 361-388, Brady. Evaluation and Management of Bradyarrhythmias in the Emergency Department.
Describes use and doses of Atropine in cases of bradycardia with cautionary statements about effects on AV conduction. Rare toxicity of worsening coronary ischemia and ventricular tachycardia were mentioned.

13. The Washington Manual of Medical Therapeutics Online, 29th edition, 1998, Lippincott, Williams and Wilkins, Carey, chapter 8. Cardiopulmonary Resuscitation and Advanced Cardiac Life Support.
Chapter on how to resuscitate notes that Atropine is used for symptomatic bradycardia and asystole. Doses recommended for bradycardia were 0.5-1.0 mg IV, repeated q3-5 min. prn; for asystole 1 mg repeated q3-5 min. Maximum dose recommended was 0.04 mg/kg.

14. Obstetrics and Gynecology, 11 (annual), 1982, p.151-173, Clark. Resuscitation of the Newborn.
Discussion of resuscitation of the newborn includes the recommendation that for the infant with bradycardia suspected due to vagal influence or any profoundly asphyxiated infant already given bicarbonate and epinephrine, a trial of Atropine 0.01-0.03 mg/kg be instituted.

15. Trauma Quarterly, vol. 12 (2), 1995, p. 133-139. Daley et al. Scientific Basis of Drugs Used in Cardiac Arrest in Trauma.
States that Atropine's use in trauma is based on its use in non-traumatic conditions such as bradycardia and asystole. Notes that full vagolytic action occurs at 0.04 mg/kg.

16. Pharmacotherapy: A Pathophysiologic Approach, 4th Edition, Appleton and Lange, 1999, p. 125-130, DiPiro et al. Chapter 9: Cardiopulmonary Resuscitation.
Textbook states that Atropine improves sinus node and AV conduction by inhibiting vagal activity, but a benefit in treating asystole has not been demonstrated in large randomized trials. For adults in asystole, 1 mg IV repeated q 3-5 minutes to a maximum dose of 3 mg was recommended (0.02 mg/kg initial dose in pediatric cases with 1 mg maximum dose in children, and 2 mg maximum in an adolescent).

17. Journal of Emergency Nursing, vol. 10 (1), Jan/Feb, 1984, p.47-49, Halpern. Pediatric Resuscitation: Making the Task Easier.
Called Atropine the drug of choice for the treatment of sinus bradycardia and used for ventricular standstill due to vagal stimulation.

18. Harrisonsonline.com:McGraw-Hill, 2000. Chapter 243: Acute myocardial Infarction.
Mentions that Atropine can be used for accelerated idioventricular rhythm and sinus bradycardia.

19. Principles and Practice of Anesthesia: St. Louis, Mosby, 1998, Longnecker et al. Chapter 34: Cardiopulmonary Resuscitation.
Textbook states that Atropine is indicated for bradycardia with hypotension, ventricular ectopy or symptoms of myocardial ischemia. Recommended adult doses were 0.05-1.0 mg IV q 3-5 minutes to a total dosage of 0.4 mg/kg. For asystole a 1 mg IV dose is proposed. It was noted that VT and VF have been caused by IV administration of Atropine.

20. Geriatrics, vol. 23 (9), 1968, p. 147-156, Marriott. Management of Cardiac Dysrhythmias Complicating Acute Myocardial Infarction.
Review article that suggests SC or IV Atropine for sinus bradycardia due to increased vagal tone and AV conduction disturbances with inadequate ventricular rate or diminished cardiac output.

21. Emergency Medicine Clinics of North America, vol. (1), April 1983, p. 3-24, Orlowski. Pediatric Cardiopulmonary Resuscitation.
A symposium on pediatric emergencies. For hemodynamically significant bradycardia (with hypotension or ventricular ectopy) Atropine is recommended at 0.01 mg/kg with a minimum 0.10 mg dose to a 2 mg maximum dose.

22. Annals of Emergency Medicine, vol. 27 (5), 1996, p. 576-587, Ornato and Peberdy. The Mystery of Bradyasystole during Cardiac Arrest.
Bradyasystole is defined as bradycardia with periods of asystole, and Atropine with transvenous pacing is suggested though it is noted that those who present this way during the initial cardiac arrest rarely survive.

23. Circulation, vol. 74 (suppl), 1986, IV-86, Paraskos. Cardiovascular Pharmacology III.
Review of cardiovascular pharmacology notes that Atropine is used for symptomatic bradycardia, AV nodal block, and ventricular asystole.

24. Archives of Internal Medicine, 1915, p.989-1007, Wilson. The Production of Atrioventricular Rhythm in Man after the Administration of Atropin.
20 subjects were given 1 mg of Atropine Sulphate parenterally. Prior to administration AV conduction disturbances could not be produced by maneuvers such as ocular pressure. Shortly after Atropine administration it was possible by such maneuvers to produce AV rhythm disturbances in 15 of the cases, but after the Atropine had reached maximum effect AV abnormalities could not be produced.

25. Virginia Medical, vol. 111, May, 1984, p.283-287, Yarbrough. Current Concepts of Cardiopulmonary Resuscitation.
In discussing treatment of cardiac arrest, author notes that use of Atropine has been suggested, but both positive and null studies of its use exist.

26. Pharmacotherapy, vol. 17 (5), 1997, p. 867-873, Rama et al. Double-blind, Randomized, Placebo-controlled Evaluation of Atropine to Prevent Vasovagal Reaction During Removal of Femoral Arterial Sheaths.
165 patients (106 men; 59 women) who were to undergo left heart catheterization were randomized to Atropine 0.5 mg or placebo IV. The purpose of the study was to determine the safety and effectiveness of Atropine in preventing vasovagal reactions (defined as having at least one of the following: heart rate reduction of 30% or decrease of 30 BPM or greater from baseline, systolic BP reduction of 30 mm Hg or more from baseline, or syncope). Of the baseline characteristics, mean diastolic BP was higher in the Atropine group at nominal significance levels. 10 vasovagal reactions were found; 2 in the Atropine group and 8 in the placebo group (p=0.03). No cardiac arrhythmias were noted. 9% of those receiving Atropine experienced a dry mouth.

iv. Counteract Surgically Induced Vagal Stimulation

a. Intraabdominal Traction.

3 reprints were provided.

1. The Pediatric Anesthesia Handbook, 2nd Edition, St. Louis, Mosby, 1997, p. 27-33, 609, Bell and Kain. Chapter:Premedication.
Already cited under "B. Uses in Anesthesia, a.Antisialogogue." Mentions traction on peritoneum as one situation were "vagolysis" may be needed.

2. Anesthesiology, vol.23, 1962, p. 365-383, Eger. Atropine, Scopolamine and Related Compounds.
Review of Atropine's clinical pharmacology with discussion of toxicity and recommendation that it be used in selected patients undergoing anesthesia.

3. Anesthesia and Analgesia, vol. 61 (2), January 1982, p. 42-45, Freisen and Lichtor. Cardiovascular Depression During Halothane Anesthesia in Infants: A Study of Three Induction Techniques.
While having no relevence to intraabdominal traction, this was an interesting randomized study of 90 healthy infants, ages 5-26 weeks who were scheduled for elective surgical procedures.
Three induction regimens were instituted. Group I: anesthesia induced by halothane in concentrations increased to 3%; Group II: Atropine 0.02 mg/kg IM prior to induction as per Group I; Group III halothane increased to 1.25% followed by IM succinylcholine, 2 mg/kg, 90 seconds after the start of induction. Nitrous Oxide was used in all groups. Hemodynamic changes in each group were ascertained and compared. Results were as follows:

Changes in Heart Rate (HR), Systolic Blood Pressure (BP), and Mean Arterial Pressure (MAP) during Three Anesthetic Induction Techniques in Infants*

	Group I	Group II	Group III
Preinduction HR	163 ± 25	198 ± 18†	168 ± 21
Lowest HR	114 ± 17	162 ± 14†	116 ± 23
% change	−30 ± 16	−18 ± 8†	−29 ± 15
Preinduction systolic BP	100 ± 15	98 ± 14	103 ± 13
Lowest systolic BP	50 ± 13†	85 ± 14	69 ± 13
% change	−50 ± 15†	−34 ± 15	−33 ± 14
Preinduction MAP	84 ± 15	95 ± 14	84 ± 13
Lowest MAP	39 ± 8†	45 ± 11	50 ± 10
% change	−54 ± 5†	−44 ± 10	−40 ± 11

* Values are means ± SD; n = 30 in each group.
† Significantly different ($p < 0.01$) from the other groups.

The authors suggest that the bradycardia and hypotension associated with halothane induction of infants can be diminished by preoperative Atropine.

b. Ocular Muscle Traction

7 references were provided.

1. Journal of Clinical Pharmacology, vol. 22, 1982, p. 477-481, Adams et al. Plasma Pharmacokinetics of Intravenously Administered Atropine in Normal Subjects.
   Previously cited under B. Uses in Anesthesia, a. Antisialogogue, and contains a statement that Atropine is used to inhibit the oculocardiac reflex associated with ophthalmic surgery.

2. Clinical Anesthesia, London, Lippincott, 1989, Barasch et al. Chapter 37: Anesthesia and the Eye.
   Textbook states that when deep inhalation anesthesia is performed in children, Atropine 0.02 mg.kg IV should be given before or shortly after induction begins. Since the oculocardiac reflex may cause bradycardia during strabismus surgery, ocular manipulation must stop before additional Atropine is given "lest even more dangerous cardiac dysrhythmias be triggered."

3. The Pediatric Anesthesia Handbook, 2nd Edition, St. Louis, Mosby, 1997, p. 27-33, 609, Bell and Kain. Chapter: Premedication.
   Previously cited under B. Uses in Anesthesia, a. Antisialogogue, and mentions strabismus surgery as one reason to give Atropine for vagolysis.

4. Anesthesiology, vol.23, 1962, p. 365-383, Eger. Atropine, Scopolamine and Related Compounds.
   Already cited under a. Intraabdominal Traction, states that pressure on the eyes may cause bradycardia which can be blocked by Atropine.

5. Principles and Practice of Anesthesia, St. Louis, Mosby, 1998, p. 2184,Longnecker et al. Part III: Specialty Areas of Practice.
   Textbook states that the oculocardiac reflex can be blocked by Atropine.

6. Principles and Practice of Anesthesia, St. Louis, Mosby, 1993, p.2243-2255, Rogers et al. Chapter 87: Anesthesia for Ophthalmologic Surgery.
   Textbook discusses the oculocardiac reflex , and for severe bradycardia recommends IV Atropine 7 ug/kg in increments.

7. Canadian Anaesthetists' Society Journal, vol. 30 (4), 1983, p. 325-326, Steward. Anticholinergic Premedication for Infants and Children.
   Editorial states that there have been more than 60 deaths due to the oculocardiac reflex as well as cases of cardiac arrest and VF. Serious complications from IV Atropine such as cardiac arrhythmias occur, but documentation is less convincing. The author concludes that Atropine is a very safe drug.

III. Discussion

Medical textbooks such as cited by the sponsor affirm that acetylcholine is an anticholinergic drug with effects on the cardiovascular, gastrointestinal, urinary, ophthalmologic systems and is antagonized by Atropine. Were that all that is needed for approval of the various requested indication, the submission would be acceptable.

By statute, adequate and well-controlled studies are needed to approve a new drug, even for drugs such as Atropine, and none were submitted. Some pharmacology studies and one phamacokinetic evaluation of IV Atropine were provided. Other than textbooks, opinions and editorials, little data were provided to support the various dosing regimens for the various overlapping indications. The various dosing regimens mentioned in the textbooks may represent practice, but the scientific basis for such regimens was not provided. While pediatric articles are provided, no pediatric clinical trials are provided. Safety information presented in many articles was not summarized.

It is true that this application is really for a change in container from glass to plastic for a drug that has been available (but not approved) for many years. Were the formulation in glass approved. this application would not require new clinical data to approve the formulation change to plastic with the already approved labeling. While that is not the case, there is a closely related approved Atropine drug product for one of the indications requested.

NDA 17106 Atropine Injection which contains 1.67 mg of Atropine equivalent to 2 mg of Atropine Sulphate was approved for the management of patients who have suffered a toxic exposure to organophosphorous or carbamate insecticides and is a listed drug. This formulation is for IM injection, and may be used prior to or after exposure. Repeat injections at unstated intervals are recommended until signs of atropinization appear. The labeling also provides a section on **Actions** which describes the antagonism of muscarinic effects by the drug. The labeling states that the drug is not for use in infants, but does not proscribe it for children. Using this approved labeling as the basis for approval under 21 CFR 314.54 (a) of Abbott's NDA for Atropine Sulphate in plastic syringes, one need only decide what differences there are in the dose, route etc. and determine if adequate information (investigations) have been provided to support the needed labeling changes. To facilitate that comparison both inserts are attached to this review.
The differences in Abbott's proposed labeling obviously contain differences in chemistry for which the sponsor has provided data under review by chemistry and microbiology. Both an adult and pediatric strengths are proposed; 0.1 and 0.05 mg/ml respectively. Subcutaneous, intramuscular and intravenous routes are mentioned in the **Description** section.

Abbott's **Clinical Pharmacology** section is more detailed than the **Actions** section of the approved drug's labeling. The AtroPen labeling states:
"Atropine antagonizes the actions of anticholinesterase agents at muscarinic neuro receptors. Atropine reduces tracheal, bronchial, and oropharyngeal secretions and relieves accompanying bronchospasm and bronchoconstriction. Atropine reduces central respiratory paralysis caused by anticholinesterase agents but is not effective in diminishing peripheral neuromuscular dysfunction."
The first two paragraphs of the Abbott proposal elaborate on Atropine's basic pharmacology and were supported by the submitted texts. The third paragraph of the labeling provides important cardiovascular information such as the observation that a small dose of Atropine can paradoxically slow the heart. However the sentence beginning "Atropine exerts a more potent...." through "Unlike the latter"which compares Atropine's actions to scopolamine should be eliminated.
The fourth and fifth paragraph provide information not provided by the AtroPen labeling about cardiovascular effects of the drug, and are supported by the texts and studies provided.
Adding these paragraphs to the approved AtroPen labeling will give a more complete description of Atropine's pharmacodynamic effects.

Missing from both labels is data on **Pharmacokinetics.** Abbott provides some description of elimination and distribution, including Atropine's presence in breast milk and the fact that it crosses the placental barrier and enters the fetal circulation. These should be retained, but data on PK should also be added. Those data can be extracted from the edrophonium plus Atropine approved labeling which provides a table of pharmacokinetic values for Atropine Sulphate as follows:

population	T1/2 hr ± S.D.	VD L/kg ± S.D.	Cl ml/kg/min ± S.D.	N	Ref.
Adults	3.0± 0.9	1.6± 0.4	6.8± 2.9	8	7
Children (.08-10 yrs)	4.8± 3.5	2.2± 1.5	6.4± 3.9	13	7
Elderly* (65-75 yrs)	10.0±7.3	1.8± 1.2	2.9± 1.9	10	7

T1/2=elimination half-life
VD=Volume of Distribution
Cl=Clearance
*No dose adjustment required because the cardiovascular effect of atropine is diminished in the elderly.

Reference 7 is Virtanen et al, Acta Anaesthesiol. Scand. 1982 : 26 :297-300.
This table is preceeded by the following paragraph which might also be incorporated into the Abbott labeling:
"Atropine Sulphate given intravenously shows first order elimination in a two compartment open model. Approximately 57% of a dose of atropine appears as unchanged drug. Tropine is the primary hepatic metabolite of atropine, and it accounts for approximately 30% of the dose. Atropine is only 14±9% bound to plasma proteins. Atropine clearance in children under 2 years and in the elderly is decreased in relation to normal healthy adults. The Biopharm review should be consulted for updates, corrections, changes etc.

No **Clinical Trials** section was provided in either insert, and given the information in this NDA no data could be cited in a new section.

In their **Indications and Usage** section Abbott has requested 10 indications, none are supported by adequate and well-controlled studies.
Using the prior approval of AtroPen, an indication for the treatment of organophosphorous or carbamate poisoning might be granted if other investigations were provided to support the necessary labeling changes. The significant changes requested include route (SC, IM, and IV versus IM for the approved product), dose ("large doses of at least 2 to 3 mg (20 to 30 ml of a 0.1 mg/ml solution) should be administered parenterally and repeated until signs of atropine intoxication appear" versus a 2 mg IM injection repeated if necessary until signs of atropinization appear for the approved product, and population (a specific pediatric dosage form is proposed by Abbott). Overlaps between the two labels are obvious, and approval for Abbott's product could be limited to 2 mg IM injections for adults as per the approved product labeling.
The 10 reprints provided by the sponsor contain one investigation, cited as number 10 in this report on page 3 by Freeman and Epstein. In that report patients who were given Atropine late, i.e. 3 hours or more post-exposure and in inadequate amounts, i.e. less than 3 mg in the first 5 hours of therapy had a 100% fatality rate compared to a 0% rate for those given prompt and adequate Atropine. While this supports the use of Atropine as per the approved label for organophosphorous poisoning, it does not establish the need for the larger doses requested by Abbott. The IV route is supported by the need for early and adequate Atropine treatment as well as the large interindividual variations when IM Atropine is given to adults (cited by Kanto and Klotz, Acta Anesthesiol Scand, 1988: 32: 69-78). One report (Drug Safety 1997 Jan: 16 (1), p. 9-47, see page 2 of this report) recommends the use of 2-5mg IV every 10-30 minutes IV for severe poisoning in adults as well as pediatric doses of 0.05-0.1 mg/kg IV. Another textbook (Ellenhorn's Medical Toxicology, second edition, Williams & Wilkins, p. 1620) suggests a dose of 2-4 mg IV for adults and 0.015-0.05 mg/kg for children repeated every 15 minutes if needed.

While there is marginal support for any change in the dosage and administration section of what is already approved, the 2 mg dose cited could be given IV as well. Additionally for more severe poisonings, doses of 2-4 mg IV Q15 minutes if needed until signs of atropinization appear seems reasonable.

More controversial would be the inclusion of a recommended pediatric dose.
Given the lack of data and consensus, it does not seem reasonable to suggest a regimen.
No other indications were supported by clinical data, but the agency has approved the fixed combination of edrophonium and Atropine for a reversal agent or antagonist of nondepolarizing neuromuscular blocking agents, and to treat the respiratory depression caused by curare overdosage. In the fixed combination ampuls there is 10 mg of edrophonium chloride and 0.14 mg of Atropine Sulphate. While Abbott has not mentioned edrophonium in its proposed dosage and administration section, they have mentioned physostigmine and neostigmine with a recommended adult Atropine dose of 1-2 mg IV for either. Physostigmine is approved for reversal of the CNS effect of drugs capable of producing the anticholinergic syndrome. Atropine is mentioned in that label as a drug to have on hand as a physostigmine antagonist. Neostigmine is approved for several indications, but the relevant one is to reverse the effects of nondepolarizing neuromuscular blocking agents (e.g. tubocurarine, metocurine, gallamine, or pancuronium) after surgery. The usual recommended dose of neostigmine is 0.5 to 2 mg, and it is recommended tha Atropine be given with or prior to neostigmine in a dose of 0.6 to 1.2 mg. Were Abbott to provide dosage forms capable of delivering appropriate doses of Atropine for neostigmine and edrophonium, approval for the additional indication of reversal of nondepolarizing neuromuscular blocking agents after surgery might be considered.
Given the dosing concerns expressed above, the **How Supplied** section should be considered next. Three single-dose syringes are proposed:
For Adults: 5 ml of 0.1 mg/ml and 10 ml of 0.1 mg/ml.
For Pediatrics: 5 ml of 0.05 mg/ ml.
To treat organophosphorous poisoning in adults at least a 2 mg dose is needed. The 5 ml package does not seem useful for this use. At least two of the 10 ml syringes would need to be used. As discussed above, for the reversal of neuromuscular blockade smaller doses would be needed, and neither package is designed to deliver smaller doses. Without an approved dose regimen in pediatrics, supplying a pediatric dosage form seems unsupported. Since pediatric dosing may well be on a mg/kg basis, this kind of fixed single- dose packaging seems insufficiently flexible for children of various sizes.

The **Contraindications** section of the AtroPen labeling state in bold that the drug is not to be used in infants. That prohibition is not included in the proposed Abbott label. Interestingly Abbott states in the **Warnings** section that children are more susceptible than adults to the toxic effects of anticholinergic agents. Unless a dosing regimen can be included for infants and children, a statement to the effect that safety and effectiveness in children has not been established might be placed in the **Precautions** section with Abbott's additional safety proviso with the contraindication for infants removed.
The AtroPen labeling notes that there are no other contraindications to the emergency use of the drug, although allergy to the drug might be stated there. Other cautions such as glaucoma, pyloric stenosis and prostatic hypertrophy can be stated in the **Precautions** section.

Under **Warnings**, the AtroPen labeling has paragraphs on the need for articial respiration and continued Atropine therapy. These might be better placed in the **Precautions** section, where additionally it is stated that patients sick enough to be treated for this condition should be placed under medical observation for a period of time.

The proposed **Carcinogenesis** and **Pregnancy** statements should be evaluated by Pharmacology, but the use here is short term and no animal data were submitted. Pregnancy category C seems to be consistent among the approved parenteral Atropine labels available.
The AtroPen section that instructs laymen how to self-administer would not be retained for the Abbott product, and since there is no **Adverse Reaction** section in the approved labeling, Abbott's section should be added.

IV. **Summary**

While the application does not provide a basis for approving any of the requested indications, there is no doubt that Atropine is an anticholinergic drug that could be useful in a variety of clinical conditions. Since an IM product is already approved for one of the requested indications, i.e. the treatment of organophosphorous poisoning, the Abbott product could be approved based on the previous approval. Under21CFR314.54 (a) changes may be made in the approved labeling based on investigations submitted. While few useful clinical studies were provided, support for an IV route and somewhat increased adult dosing in severe organophosphorous poisoning might be granted. Unfortunately, no pediatric dosing recommendation could be made, and thought needs to be given as to how to develop information sufficient to support pediatric dosing recommendations. While a pediatric formulation was proposed for marketing that would need to be deferred until such time as labeling is revised to include pediatric dosing. Draft labeling based on the already approved labeling follows.

V. **Proposed Labeling**

ATROPINE SULFATE
DRAFT

DRAFT

5 pages redacted from this section of the approval package consisted of draft labeling

(PP. 19-23)

FEB - 4 2000

To: NDA 21-146 SF 2/4/00
From: Stephen Fredd, M.D.
Subject: Filing Consideration Re: Medical Portion

This NDA was submitted by Abbott on 12/16/1999. It is for approval of Atropine Sulfate Injections, USP, Plastic syringes (0.1mg/ml in a 10 ml or 5 ml syringe, and 0.05 mg/ml in a 5 ml syringe) for the following indications:
1. antisialogogue for preanesthetic medication to prevent or reduce respiratory tract secretions.
2. to restore cardiac rate and arterial pressure during anesthesia when vagal stimulation produced by intraabdominal surgical traction causes a sudden decrease in pulse rate and cardiac action.
3. to lessen the degree of A-V heart block when increased vagal tone is a major factor in the conduction defect as in some cases due to digitalis.
4. to overcome severe bradycardia and syncope due to a hyperactive carotid sinus reflex.
5. as an antidote (with external cardiac message) for cardiovascular collapse from the injudicious use of a choline ester (cholinergic) drug.
6. in the treatment of anticholinesterase poisoning from organophosphorous insecticides.
7. as an antidote for the "rapid" type of mushroom poisoning due to the presence of the alkaloid, muscarine, in certain species of fungus such as Amanita muscaria.

An NDA for an IM injection of atropine sulfate (2 mg) for management of patients with a toxic exposure to organophosphorous or carbamate insecticides has been approved. Since atropine is a pre-1938 drug, Abbott has been marketing Atropine Sulfate Injection in glass without an approved NDA. The strength of their products differ from the approved product, and their product could be given SC, IM, or IV. While they have not and sought approval for atropine in glass containers, which continues to be marketed for the above listed indications, a change to plastic containers does require NDA approval. Correspondance from the agency to Abbott, including a response to a Citizen Petition, indicated that a 505(b)2 application might be submitted (rather than a 505(j) application), and that is the application to be considered for filing.

For the medical portion of this NDA, the sponsor has provided the results of a literature search covering the years 1915-1999. Keywords used in the search included "atropine sulfate-administration, dosage, toxicity, therapeutic use and clinical use." Nineteen references were provided, and are listed on the attachment to this memo.
The references included two pharmacokinetic studies (Kanto, J., Kloth, U. 1988. Pharmacokinetic implications for the clinical use of atropine, scopolamine, and glycopyrrolate. Acta Anaesthesiologica Scandinavica, 32:69-78 and Adams et al, 1982. Plasma pharmacokinetics of intravenously administered atropine in normal human subjects. Journal of Clinical Pharmacology, 22: 477-481), one.
There is retrospective chart review of patients with myocardial infarction (Adgey et al, 1968. Incidence, significance and management of early bradyarrhythmia complicating acute myocardial infarction. The Lancet, 2 (7578): 1097-1101), 3 case study articles (Wilson, FN. 1915. The production of atrioventricular rhythm in man after the administration of atropin. Archives of Internal Medicine, 16: 989-1007; Navab, F. 1967. Self-poisoning with digitalis glycosides. British Medical Journal, 3 (566): 661-662; and Norris, RM. 1969. Bradyarrhythmia after myocardial infarction. The Lancet, 1 (7589): 313-314).
One randomized controlled clinical trial was provided: an active controlled study of pethidine and promethizine alone versus those drugs plus atropine as premedications for routine adult anesthesia. No significant differences between the regimens were noted.
The other references were review articles.
To support safety the sponsor reviewed reports of adverse events and found none.
No preclinical or clinical pharmacology information was provided.

Filing evaluation:
For the medical portion of this NDA, no adequate and well-controlled studies that might support the indications could be identified. While I would recommend that the application in its current form not be filed, we should work with the sponsor to explore ways that they might gain approval for this product.

CC:Dr.Lipicky
Diana Willard

Medical Literature References

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Medical Literature References (Cont'd)

PEDIATRIC REFERENCES

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2. Orlowski, J. 1983. Pediatric cardiopulmonary resuscitation. *Emergency Clinics of North America: 8(6)*, 3-25.

3. Steward, DJ. 1983. Anticholinergic premedication for infants and children. *Canadian Anaesthetists' Society Journal, 30(4):* 325-8.

Section II. Summary

Atropine Sulfate Injection, USP, is a sterile, nonpyrogenic, isotonic solution of atropine sulfate in water for injection with sodium chloride sufficient to render the solution isotonic. It is administered parenterally by subcutaneous, intramuscular or intravenous injection.

Atropine Sulfate Injection is an anticholinergic agent and muscarininc antagonist. The drug products packaged in either 5 mL or 10 mL Unit of Use plastic syringe are aqueous, terminally sterilized drug products containing no bacteriostat or antimicrobial agent. It may contain hydrochlorid acid and/or sodium hydroxide for pH adjustment.

Atropine Sulfate Injection, USP, is currently marketed for the treatment (1) as an antisialogogue for preanesthetic medication to prevent or reduce secretions of the respiratory tract, (2) to restore cardiac rate and arterial pressure during anesthesia when vagal stimulation produced by intra-abdominal surgical traction causes a sudden decrease in pulse rate and cardiac action, (3) to lessen the degree of atrioventricular (A-V) heart block when increased vagal tone is major factor in the conduction defect as in some cases due to digitalis, (4) to overcome severe bradycardia and syncope due to a hyperactive carotid sinus reflex, (5) as an antidote (with external cardiac massage) for cardiovascular collapse from the injudicious use of a choline ester (cholinergic) drug, (6) in the treatment of anticholinesterase poisoning from organophosphorus insecticides, and (7) as an antidote for the "rapid" type of mushroom poisoning due to the presence of the alkaloid, muscarine, in certain species of fungus such as *Amanita muscaria*.

Atropine Sulfate Injection, USP, 0.1 mg/mL and 0.05 mg/mL, are currently marketed in glass containers. These products were on the market in 1938 and wrer grandfathered under the 1938 Food, Drug & Cosmetic Act. Abbott Laboratories markets these products in the glass container under the brand name of ABBOJECT®. It would be beneficial to the public to offer these injectable drugs in plastic syringes, e.g., Ansyr® Syringe.

The dosage forms and manufacturing site may be described as follows:

List Number	Concentration	Fill Volume	Size/ Type Container	Manufacturing Facility
1630	0.1 mg/mL	10 mL	10 mL Plastic Syringe	
9629	0.1 mg/mL	5 mL	5 mL Plastic Syringe	
9630	0.05 mg/mL	5 mL	5 mL Plastic Syringe	

The change from a glass to a plastic container has no effect on safety or efficacy of the Atropine Sulfate Injection, USP or on the indications described in the proposed labeling. Literature references support the medical indications of this drug product.

The plastic syringe is molded from a specially formulated Water permeates from inside the container at an extremely slow rate which will have an insignificant effect on solution concentration over the expected shelf life. Solution in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the syringe material.